REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-22 are in the case.

I. THE INTERVIEW

At the outset, the undersigned wishes to thank the Examiner (Mr. Snedden) for kindly agreeing to conducting a telephonic interview in this application. The interview was held on December 1, 2003 and was attended by Dr. Jenny Petering, an Australian patent attorney representing the assignee as well as by the undersigned. The courtesies extended by the Examiner during the interview were most appreciated. The substance of the interview will be clear from the comments presented below.

II. THE PRIOR ART REJECTIONS

Claims 1-22 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 4,789,733 to Winkelman in view of Mosesson and Altieri et al (U.S. 20020131970 A1). That rejection is respectfully traversed.

As explained in our previous response, the present invention is based on the surprising finding that high levels of fibrinogen can be extracted from a heparin induced precipitate by resolubilzation with a solution containing at least 0.1 M salt. Accordingly, the present claims are directed a **two** step method to produce a fibrinogen enriched preparation, comprising:

(i) adding an effective amount of a sulphated polysaccharide (SPS) to a fibrinogen containing solution to form a precipitate containing fibrinogen; and

(ii) extracting fibrinogen from the precipitate containing fibrinogen from step (i) with a solution containing at least 0.1M salt to obtain a fibrinogen enriched preparation.

As discussed during the interview, Winkelman is directed to preparing factor VIII (FVIII). This method involves removal of fibrinogen and fibronectin from blood plasma fractions, while leaving blood coagulation factor VIII in the supernatant. The specification indicates that previous methods of purifying FVIII have been hampered by the presence of fibrinogen and fibronectin in the plasma fractions which tend to make those fractions sticky and viscous. Thus, Winkelman is directed towards the separation of FVIII from the fibronectin/fibrinogen components in the blood.

The first step of Winkelman's method involves the addition of high concentrations of sulphated polysaccharide (e.g. heparin) to a blood plasma fraction, which causes the selective precipitation of fibrinogen/fibronectin, while leaving FVIII in the supernatant. Winkelman found that the addition of high concentrations of heparin to a blood plasma fraction causes the precipitation of fibrinogen and fibronectin. Before this discovery, quite the opposite was thought, and low concentrations of heparin were widely used as an anticoagulant of blood and blood products.

Winkelman is acknowledged in the present application in the paragraph bridging pages 5 and 6, and is encompassed by step (i) of claim 1. However, this is where the overlap between the Winkelman disclosure and the present invention ends. Winkelman used heparin precipitation to remove fibrinogen/fibronectin from blood plasma fractions. The fibrinogen/fibronectin precipitate formed at this stage was discarded by Winkelman as she was interested in further purification of FVIII from the supernatant. Winkelman does note, in passing, that the fibrinogen/fibronectin precipitate "may be discarded or

may be further processed to extract the fibronectin (which is becoming of increasing clinical interest) and the fibrinogen" (column 6, lines 1 to 3). However, as noted during the interview, Winkelman does not disclose or suggest how to perform such an extraction.

This is where the present invention provides an important advance. The present invention essentially takes the "discarded" precipitate which is a by-product of the Winkelman process for producing FVIII, and enables, for the first time, efficient extraction from the precipitate of commercially important fibrinogen from this precipitate.

The Examiner's comments with respect to Example 23 of Winkelman were discussed during the interview. It was pointed out, first, that Example 23 is a "comparative" example and, therefore, does not involve the inventive concept of using heparin to precipitate fibrinogen from blood plasma. The steps of the process described in Example 23 of Winkelman are set out in Figure 1 below.

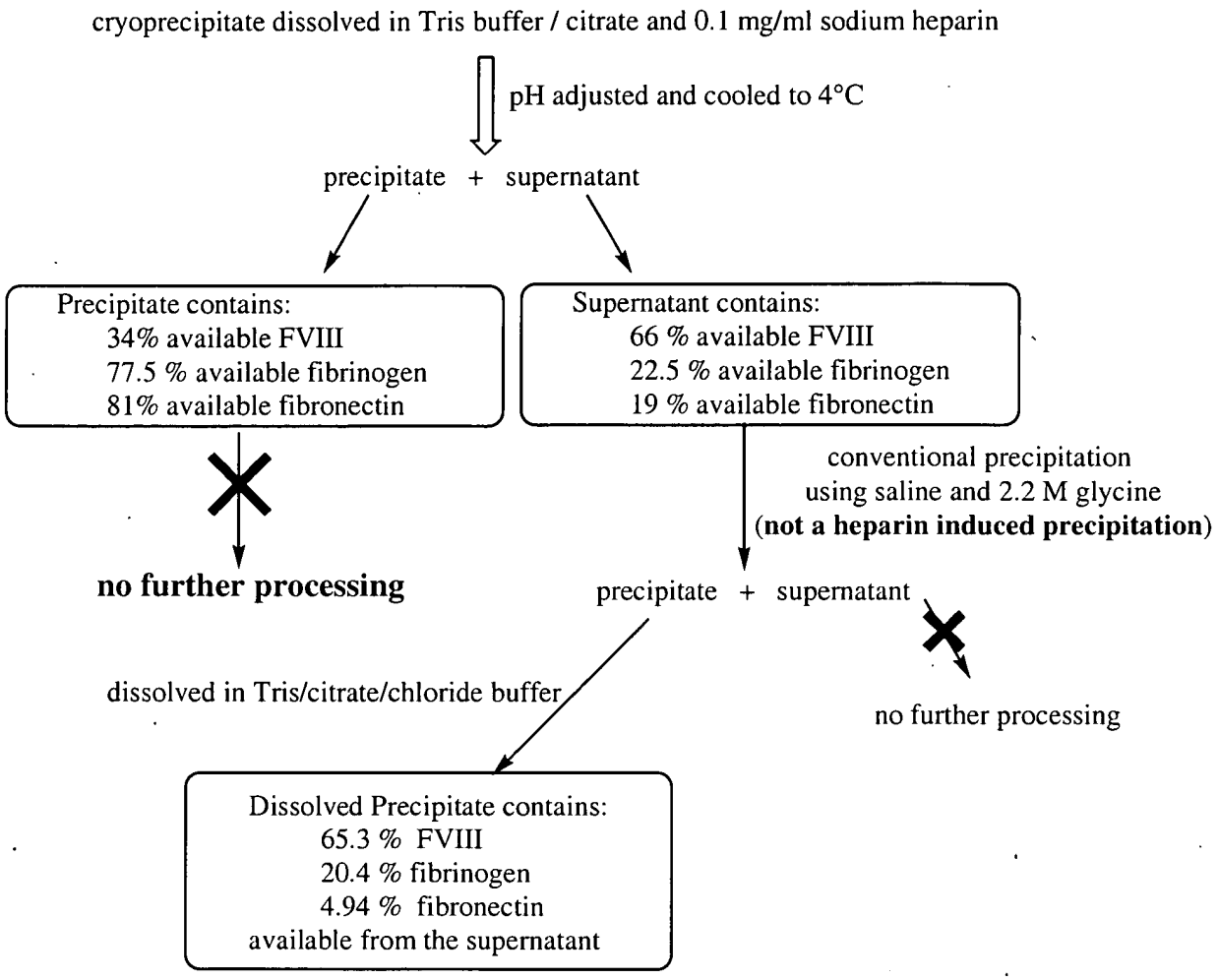

Figure 1. Flowchart of Comparative Example 23

In Example 23, a cryoprecipitate is dissolved in Tris buffer containing 20 mM Na_3citrate, 0.1 M sodium heparin and 30 u/ml aprotinin. The citrate and heparin components are in anticoagulant concentrations and the aprotinin is an added protease inhibitor. The precipitation is effected by cooling the solution to +4°C, and the precipitate containing over 75% of the fibrinogen and 81% of the available fibronectin is removed and is not processed further.

The FVIII containing supernatant is then subjected to conventional precipitation conditions by the addition of saline/2.2 M glycine solution. The resulting precipitate is then solubilized in a tris/citrate/chloride buffer. As noted during the interview, this precipitate is not formed by adding an effective amount of a sulphated polysaccharide, and it is not the same precipitate as is required by claim 1 of the present application.

Example 23 clearly does not disclose or suggest the two step method for making a fibrinogen enriched preparation as claimed in claim 1 of the present application. Example 23 of Winkelman is entirely directed towards producing a FVIII enriched preparation which contains as little fibrinogen or fibronectin as possible.

Thus the main points of distinction between Example 23 and the present application are:

i) there is not a step of adding an effective amount of a sulphated polysaccharide; instead the precipitation is performed by reducing the temperature;

ii) the fibrinogen containing precipitate is discarded and is not further processed;

iii) the supernatant containing primarily FVIII is processed by a further precipitation, which does not involve the addition of an effective amount of a sulphated polysaccharide, but instead involves the addition of a saline/2.2 M glycine solution **to precipitate out the FVIII and leave the fibrinogen and fibronectin in solution.**

Contrary to the Examiner's assertion, Example 23 does not disclose or suggest how to further process a heparin induced precipitate, as the precipitation in Example 23 is not induced by the addition of heparin. The precipitation is in fact either performed by (i) cooling the solution to 4°C or (ii) by adding saline and 2.2 M glycine.

Example 24 of Winkelman involves the steps as presented in Figure 2 below. In Example 24, Winkelman describes the use of a sodium heparin solution to effect the selective precipitation of fibrinogen/fibronectin over FVIII (equivalent to step (i) of the present claims). However, unlike the present claims, Winkelman **discards** the precipitate, and concentrates on the supernatant which contains predominately FVIII. The further processing of the supernatant does not involve the addition of heparin (heparin is already in the solution). Rather it involves "conventional precipitation, using a saline, 2.2M glycine solution" (see column 11, lines 45 to 47 which refers back to Example 23). The precipitate formed by the addition of saline and 2.2M glycine is isolated and dissolved in a tris/citrate/chloride solution. The supernatant is discarded.

Thus Example 24 of Winkelman does not disclose or suggest extracting fibrinogen from a precipitate formed by the addition of heparin using a solution containing at least 0.1 M salt. On the contrary, Example 24 discards the heparin induced precipitate containing fibrinogen and concentrates on conducting a further precipitation step using **saline and 2.2M glycine** solution to obtain purified FVIII.

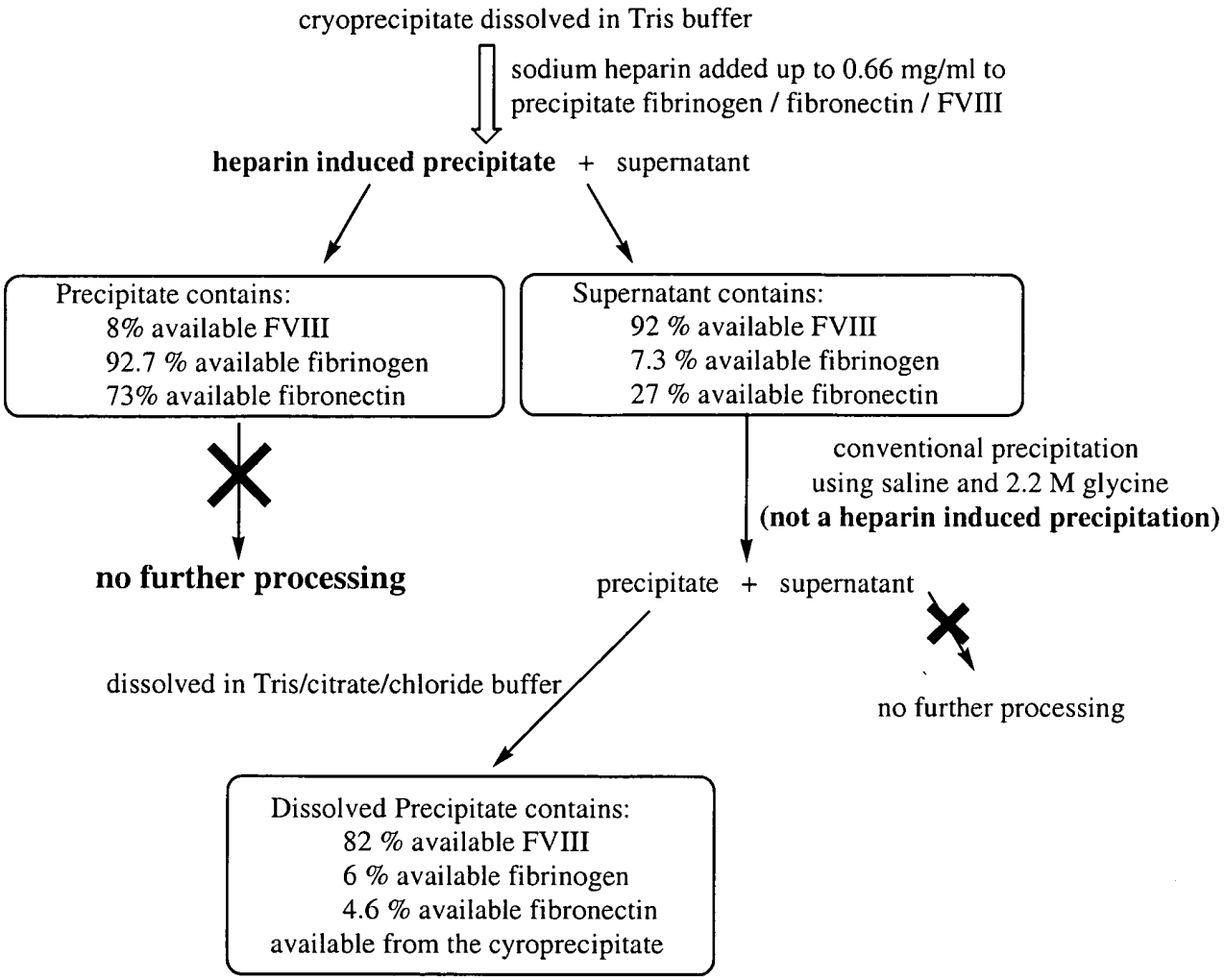

Figure 2. Flowchart of Example 24

Example 24 clearly does not disclose or suggest both steps (i) and (ii) as claimed in the present case. Example 24 is directed towards extracting a FVIII preparation from a supernatant using conventional precipitation techniques, and the preparation is said to contain as little fibrinogen and fibronectin as possible.

Mosesson does not cure the deficiencies of Winkelman. Indeed, Mosesson actively teaches **away** from the present claims. In particular, Mosesson teaches away

from step (i) as claimed, as the paper specifically discloses that the addition 95% ethanol to a 0.3 M NaCl solution of fibrinogen and plasminogen will effect the precipitation. Thus, Mosesson discloses that the presence of a salt such as NaCl is necessary for the precipitation of the fibrinogen. This is in contrast to the presently claimed invention.

Moreover, there would have been no motivation for a person skilled in the art to combine the disclosures of Winkelman and Mosesson to arrive at the presently claimed invention. Winkelman is directed to a method of purifying FVIII from blood plasma, whereas Mosesson is directed to the preparation of plasminogen free fibrinogen. These processes are clearly distinct, and a person skilled in the art would not have looked to combine individual steps from these processes to develop a method for purifying fibrinogen. In any case, the combined disclosures do not lead to the method as claimed in the present application.

Altieri likewise fails to address the deficiencies of Winkelman. Altieri describes, *inter alia*, a process for the isolation of fibrinogen by the addition of cold 50% ethanol to a plasma, and collecting the precipitated fibrinogen. The ethanol affected precipitation was repeated several times to produce a purified fibrinogen preparation. Any remaining fibronectin was then removed by passage through a gelatin Sepharose 4B column. There would have been no motivation for one of ordinary skill to combine the disclosure of Winkelman with that of Altieri.

Withdrawal of the obviousness rejection based on the combined disclosures Winkelman, Mosesson and Altieri is now believed to be in order. Such action is requested.

Claims 1 to 22 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Amrani (US Patent 4,278,594). This rejection is respectfully traversed.

Amrani describes a process for the separation and isolation of anti-hemophilia factor (AHF), fibronectin and von Willebrands ristocetin cofactor from blood plasma. The method involves the addition of sodium heparin to human blood plasma and stirring the solution until the materials are completely dissolved (Example 2). The solution is then cooled at 4°C for 18 hours to effect the precipitation.

As noted during the interview, in Amrani's method, the fibrinogen containing precipitate is washed with 1000 ml of a 0.5 M NaH_2PO_4 and 0.1 NaCl solution. The washings are then discarded (see column 4, lines 12 to 14). The resulting precipitate is **dissolved** in 0.05 M KI, 0.1M Tris, and chromatography is then employed to separate the fibronectin "**from the dissolved precipitate**" (column 5, lines 38-40; emphasis added). Amrani contains no disclosure or suggestion of extracting fibrinogen "from the precipitate containing fibrinogen from step (i)...", as required by the presently claimed method.

The Examiner notes that Amrani's first step in the extraction process was to ***wash*** the fibrinogen containing precipitate with dilute salts. As noted during the interview, the purpose of the washing step is to remove impurities from the precipitate **without** the loss of fibrinogen from the precipitate. This is in contrast to step (ii) of the presently method where at least a 0.1 M salt solution is used to ***extract*** fibrinogen from the precipitate. As pointed out above, the washings in the Amrani process are discarded. A skilled addressee would assume, therefore, that the washing step does

not result in efficient extraction of fibrinogen from the precipitate. In this regard the Amrani disclosure leads **away** from the present invention.

Withdrawal of the anticipation rejection based on Amrani is now believed to be in order. Such action is requested.

Claims 1 to 22 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Amrani in view of Mosesson and Altieri. In response, Amrani is believed to be irrelevant for the reasons discussed above. Mosesson and Altieri do not cure the deficiencies of Amrani, for the reasons discussed earlier with respect to Mosesson and Altieri. Withdrawal of this rejection is accordingly respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

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